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Applicant : Ashkenazi et al.

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POLYPEPTIDES AND NUCLEIC
ACIDS ENCODING THE SAME

Examiner : Hamud, Fozia M

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DECLARATION OF AVI ASHKENAZI, Ph.D UNDER 37 C.F.R. § 1.132

I, Avi Ashkenazi, Ph.D. declare and say as follows: -

1. I am Director and Staff Scientist at the Molecular Oncology Department of Genentech, Inc., South San Francisco, CA 94080.
2. I joined Genentech in 1988 as a postdoctoral fellow. Since then, I have investigated a variety of cellular signal transduction mechanisms, including apoptosis, and have developed technologies to modulate such mechanisms as a means of therapeutic intervention in cancer and autoimmune disease. I am currently involved in the investigation of a series of secreted proteins over-expressed in tumors, with the aim to identify useful targets for the development of therapeutic antibodies for cancer treatment.
3. My scientific Curriculum Vitae, including my list of publications, is attached to and forms part of this Declaration (Exhibit A).
4. Gene amplification is a process in which chromosomes undergo changes to contain multiple copies of certain genes that normally exist as a single copy, and is an important factor in the pathophysiology of cancer. Amplification of certain genes (e.g., Myc or Her2/Neu)

gives cancer cells a growth or survival advantage relative to normal cells, and might also provide a mechanism of tumor cell resistance to chemotherapy or radiotherapy.

5. If gene amplification results in over-expression of the mRNA and the corresponding gene product, then it identifies that gene product as a promising target for cancer therapy, for example by the therapeutic antibody approach. Even in the absence of over-expression of the gene product, amplification of a cancer marker gene - as detected, for example, by the reverse transcriptase TaqMan[®] PCR or the fluorescence *in situ* hybridization (FISH) assays - is useful in the diagnosis or classification of cancer, or in predicting or monitoring the efficacy of cancer therapy. An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes.

6. I understand that according to the Patent Office, absent data demonstrating that the increased copy number of a gene in certain types of cancer leads to increased expression of its product, gene amplification data are insufficient to provide substantial utility or well established utility for the gene product (the encoded polypeptide), or an antibody specifically binding the encoded polypeptide. However, even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so

made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

By: Avi Ashkenazi
Avi Ashkenazi, Ph.D.

Date: 9/15/03

CURRICULUM VITAE

Avi Ashkenazi

July 2003

Personal:

Date of birth: 29 November, 1956
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Education:

1983: B.S. in Biochemistry, with honors, Hebrew University, Israel
1986: Ph.D. in Biochemistry, Hebrew University, Israel

Employment:

1983-1986: Teaching assistant, undergraduate level course in Biochemistry
1985-1986: Teaching assistant, graduate level course on Signal Transduction
1986 - 1988: Postdoctoral fellow, Hormone Research Dept., UCSF, and
Developmental Biology Dept., Genentech, Inc., with J. Ramachandran
1988 - 1989: Postdoctoral fellow, Molecular Biology Dept., Genentech, Inc.,
with D. Capon
1989 - 1993: Scientist, Molecular Biology Dept., Genentech, Inc.
1994 -1996: Senior Scientist, Molecular Oncology Dept., Genentech, Inc.
1996-1997: Senior Scientist and Interim director, Molecular Oncology Dept.,
Genentech, Inc.
1997-1990: Senior Scientist and preclinical project team leader, Genentech, Inc.
1999 -2002: Staff Scientist in Molecular Oncology, Genentech, Inc.
2002-present: Staff Scientist and Director in Molecular Oncology, Genentech, Inc.

Awards:

1988: First prize, The Boehringer Ingelheim Award

Editorial:

Editorial Board Member: Current Biology
Associate Editor, Clinical Cancer Research.
Associate Editor, Cancer Biology and Therapy.

Refereed papers:

1. Gertler, A., Ashkenazi, A., and Madar, Z. Binding sites for human growth hormone and ovine and bovine prolactins in the mammary gland and liver of the lactating cow. *Mol. Cell. Endocrinol.* **34**, 51-57 (1984).
2. Gertler, A., Shamay, A., Cohen, N., Ashkenazi, A., Friesen, H., Levanon, A., Gorecki, M., Aviv, H., Hadari, D., and Vogel, T. Inhibition of lactogenic activities of ovine prolactin and human growth hormone (hGH) by a novel form of a modified recombinant hGH. *Endocrinology* **118**, 720-726 (1986).
3. Ashkenazi, A., Madar, Z., and Gertler, A. Partial purification and characterization of bovine mammary gland prolactin receptor. *Mol. Cell. Endocrinol.* **50**, 79-87 (1987).
4. Ashkenazi, A., Pines, M., and Gertler, A. Down-regulation of lactogenic hormone receptors in Nb2 lymphoma cells by cholera toxin. *Biochemistry Internatl.* **14**, 1065-1072 (1987).
5. Ashkenazi, A., Cohen, R., and Gertler, A. Characterization of lactogen receptors in lactogenic hormone-dependent and independent Nb2 lymphoma cell lines. *FEBS Lett.* **210**, 51-55 (1987).
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7. Peralta, E., Winslow, J., Peterson, G., Smith, D., Ashkenazi, A., Ramachandran, J., Schimerlik, M., and Capon, D. Primary structure and biochemical properties of an M2 muscarinic receptor. *Science* **236**, 600-605 (1987).
8. Peralta, E., Ashkenazi, A., Winslow, J., Smith, D., Ramachandran, J., and Capon, D. J. Distinct primary structures, ligand-binding properties and tissue-specific expression of four human muscarinic acetylcholine receptors. *EMBO J.* **6**, 3923-3929 (1987).
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10. Pines, M., Ashkenazi, A., Cohen-Chapnik, N., Binder, L., and Gertler, A. Inhibition of the proliferation of Nb2 lymphoma cells by femtomolar concentrations of cholera toxin and partial reversal of the effect by 12-o-tetradecanoyl-phorbol-13-acetate. *J. Cell. Biochem.* **37**, 119-129 (1988).
11. Peralta, E., Ashkenazi, A., Winslow, J., Ramachandran, J., and Capon, D. Differential regulation of PI hydrolysis and adenylyl cyclase by muscarinic receptor subtypes. *Nature* **334**, 434-437 (1988).
12. Ashkenazi, A., Peralta, E., Winslow, J., Ramachandran, J., and Capon, D. Functionally distinct G proteins couple different receptors to PI hydrolysis in the same cell. *Cell* **56**, 487-493 (1989).
13. Ashkenazi, A., Ramachandran, J., and Capon, D. Acetylcholine analogue stimulates DNA synthesis in brain-derived cells via specific muscarinic acetylcholine receptor subtypes. *Nature* **340**, 146-150 (1989).
14. Lammare, D., Ashkenazi, A., Fleury, S., Smith, D., Sekaly, R., and Capon, D. The MHC-binding and gp120-binding domains of CD4 are distinct and separable. *Science* **245**, 743-745 (1989).
15. Ashkenazi, A., Presta, L., Marsters, S., Camerato, T., Rosenthal, K., Fendly, B., and Capon, D. Mapping the CD4 binding site for human immunodeficiency virus type 1 by alanine-scanning mutagenesis. *Proc. Natl. Acad. Sci. USA.* **87**, 7150-7154 (1990).
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17. Ashkenazi, A., Smith, D., Marsters, S., Riddle, L., Gregory, T., Ho, D., and Capon, D. Resistance of primary isolates of human immunodeficiency virus type 1 to soluble CD4 is independent of CD4-gp120 binding affinity. *Proc. Natl. Acad. Sci. USA.* **88**, 7056-7060 (1991).
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21. Marsters, A., Frutkin, A., Simpson, N., Fendly, B. and Ashkenazi, A. Identification of cysteine-rich domains of the type 1 tumor necrosis receptor involved in ligand binding. *J. Biol. Chem.* 267, 5747-5750 (1992).
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27. Chamow, S., Zhang, D., Tan, X., Mhtre, S., Marsters, S., Peers, D., Byrn, R., Ashkenazi, A., and Yunghans, R. A humanized bispecific immunoadhesin-antibody that retargets CD3+ effectors to kill HIV-1-infected cells. *J. Immunol.* 153, 4268-4280 (1994).
28. Means, R., Krantz, S., Luna, J., Marsters, S., and Ashkenazi, A. Inhibition of murine erythroid colony formation in vitro by interferon γ and correction by interferon γ receptor immunoadhesin. *Blood* 83, 911-915 (1994).
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34. Oksenberg, D., Havlik, S., Peroutka, S., and Ashkenazi, A. The third intracellular loop of the 5-HT₂ receptor specifies effector coupling. *J. Neurochem.* 64, 1440-1447 (1995).
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41. Marsters, S., Skubatch, M., Gray, C., and Ashkenazi, A. Herpesvirus entry mediator, a novel member of the tumor necrosis factor receptor family, activates the NF- κ B and AP-1 transcription factors. *J. Biol. Chem.* 272, 14029-14032 (1997).
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45. Rieger, J., Naumann, U., Glaser, T., Ashkenazi, A., and Weller, M. Apo2 ligand: a novel weapon against malignant glioma? *FEBS Lett.* 427, 124-128 (1998).
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47. Pitti, R., Marsters, S., Lawrence, D., Roy, Kischkel, F., M., Dowd, P., Huang, A., Donahue, C., Sherwood, S., Baldwin, D., Godowski, P., Wood, W., Gurney, A., Hillan, K., Cohen, R., Goddard, A., Botstein, D., and Ashkenazi, A. Genomic amplification of a decoy receptor for Fas ligand in lung and colon cancer. *Nature* 396, 699-703 (1998).
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53. Roth, W., Isenmann, S., Naumann, U., Kugler, S., Bähr, M., Dichgans, J., Ashkenazi, A., and Weller, M. Eradication of intracranial human malignant glioma xenografts by Apo2L/TRAIL. *Biochem. Biophys. Res. Commun.* 265, 479-483 (1999).
54. Hymowitz, S.G., Christinger, H.W., Fuh, G., Ultsch, M., O'Connell, M., Kelley, R.F., Ashkenazi, A. and de Vos, A.M. Triggering Cell Death: The Crystal Structure of Apo2L/TRAIL in a Complex with Death Receptor 5. *Molec. Cell* 4, 563-571 (1999).
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56. Zhou, Q., Fukushima, P., DeGraff, W., Mitchell, J.B., Stetler-Stevenson, M., Ashkenazi, A., and Steeg, P.S. Radiation and the Apo2L/TRAIL apoptotic pathway preferentially inhibit the colonization of premalignant human breast cancer cells overexpressing cyclin D1. *Cancer Res.* 60, 2611-2615 (2000).
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58. Yan, M., Marsters, S.A., Grewal, I.S., Wang, H., *Ashkenazi, A., and *Dixit, V.M. Identification of a receptor for BlyS demonstrates a crucial role in humoral immunity. *Nature Immunol.* 1, 37-41 (2000).

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60. Kischkel, F.C., and Ashkenazi, A. Combining enhanced metabolic labeling with immunoblotting to detect interactions of endogenous cellular proteins. *Biotechniques* 29, 506-512 (2000).
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Review articles:

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2. Ashkenazi, A., Peralta, E., Winslow, J., Ramachandran, J., and Capon, D. Functional diversity of muscarinic receptor subtypes in cellular signal transduction and growth. *Trends Pharmacol. Sci.* Dec Supplement, 12-21 (1989).
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4. Ashkenazi, A., Capon, and D. Ward, R. Immunoadhesins. *Int. Rev. Immunol.* **10**, 217-225 (1993).
5. Ashkenazi, A., and Peralta, E. Muscarinic Receptors. In *Handbook of Receptors and Channels*. (S. Peroutka, ed.), CRC Press, Boca Raton, Vol. I, p. 1-27, (1994).
6. Krantz, S. B., Means, R. T., Jr., Lina, J., Marsters, S. A., and Ashkenazi, A. Inhibition of erythroid colony formation in vitro by gamma interferon. In *Molecular Biology of Hematopoiesis* (N. Abraham, R. Shadduck, A. Levine F. Takaku, eds.) Intercept Ltd. Paris, Vol. 3, p. 135-147 (1994).
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12. Ashkenazi, A., and Dixit, V. Apoptosis control by death and decoy receptors. *Curr. Opin. Cell. Biol.* **11**, 255-260 (1999).

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14. Ashkenazi, A. Targeting death and decoy receptors of the tumor necrosis factor superfamily. *Nature Rev. Cancer* 2, 420-430 (2002).
15. LeBlanc, H. and Ashkenazi, A. Apoptosis signaling by Apo2L/TRAIL. *Cell Death and Differentiation* 10, 66-75 (2003).
16. Almasan, A. and Ashkenazi, A. Apo2L/TRAIL: apoptosis signaling, biology, and potential for cancer therapy. *Cytokine and Growth Factor Reviews* 14, 337-348 (2003).

Book:

Antibody Fusion Proteins (Chamow, S., and Ashkenazi, A., eds., John Wiley and Sons Inc.) (1999).

Talks:

1. Resistance of primary HIV isolates to CD4 is independent of CD4-gp120 binding affinity. UCSD Symposium, HIV Disease: Pathogenesis and Therapy. Greenelefe, FL, March 1991.
2. Use of immuno-hybrids to extend the half-life of receptors. IBC conference on Biopharmaceutical Half-life Extension. New Orleans, LA, June 1992.
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11. Apo2 ligand, an extracellular trigger of apoptosis. 2nd Clontech Symposium, Palo Alto, CA, October 1996.
12. Regulation of apoptosis by members of the TNF ligand and receptor families. Stanford University School of Medicine, Palo Alto, CA, December 1996.
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